# Endoscopic and Histologic Findings in Pediatric Inflammatory Bowel Disease

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**Abstract:** Inflammatory bowel disease (IBD) is an increasingly important cause of gastrointestinal pathology in children. Approximately 25% of IBDs present before the patient is 20 years of age. Accurate diagnosis and differentiation between Crohn's disease (CD) and ulcerative colitis (UC) is important in planning treatment strategies, particularly in children. Endoscopy, which allows direct visualization of gastrointestinal mucosa and biopsy of multiple sites, is an integral part of this diagnostic process. Although no endoscopic lesion is pathognomonic of IBD, certain features are highly suggestive of either CD or UC. In this article, we review and attempt to correlate endoscopic and histologic findings in IBD that have particular emphasis on the pediatric population.

Inflammatory bowel disease (IBD) includes Crohn's disease (CD), ulcerative colitis (UC), and IBDs without differentiating features (undecided or indeterminate colitis [IC]). These entities differ in clinical presentation, distribution of inflammation in the gastrointestinal tract, progression of disease, and response to interventions, either medical or surgical. Up to 25% of IBD patients present before 20 years of age.[1] Presentations in the pediatric population may differ from those seen in adults. Unique features in children include growth failure and pubertal delay, which must be considered when planning treatment.[2] Clear diagnosis of IBD and differentiation of CD from UC and/or IC is essential in planning the optimal treatment strategy in a given patient. Recommendations from the European and North American pediatric gastroenterology societies have helped bring uniformity in the diagnostic work-up and the differentiation of IBD types. Gastroenterologists and pathologists involved in pediatric care have been well served by these recent consensus reviews.[3,4]

IBD, as its name implies, is characterized by involvement of the gastrointestinal tract, with CD affecting the small and large bowels as well as the upper gastrointestinal tract. In contrast, inflammation in UC is generally considered to be limited to the colonic mucosa.[5,6]

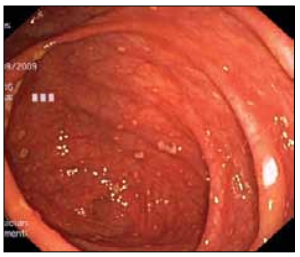

**Figure 1.** Aphthous ulcers in early colonic Crohn's disease.

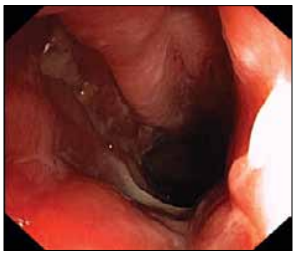

**Figure 2.** Deep serpigous ulcers in established Crohn's disease.

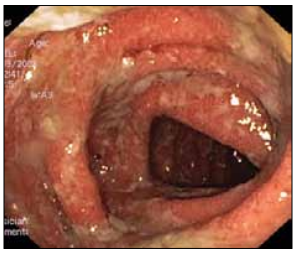

**Figure 3.** Ulcerative colitis showing diffuse erythema and contiguous superficial ulcerations.

Childhood CD is anatomically progressive in one third of patients. Although they are less common in younger patients, stricture and fistula formation may complicate the disease course as well.[6,7] Childhood CD has also been shown to have rapid early progression, often with ileal involvement, particularly in children older than 8 years of age.[6] In UC, inflammation is diffuse, contiguous, and superficial, beginning at the rectum and extending proximally. In children, the distribution of inflammation in the colon is extensive, with the recorded frequency of pancolitic UC greater than that of adults.[8-11] Although in the majority of cases the differentiation of CD from UC is relatively straightforward with the help of clinical, radiographic, endoscopic, and histologic findings, in up to 30% of cases a clear distinction is not possible, and a diagnosis of IC is considered.[12]

## Endoscopy

Although endoscopic appearances are not always specific enough to differentiate between CD and UC, some features can favor one diagnosis over the other.[13] For instance, aphthous ulcers may be seen early, and then may progress to large linear and deep serpiginous "bear claw" ulcers (Figures 1 and 2). Submucosal inflammation and edema may lead to a cobblestone appearance of the mucosal surface. Skip lesions (disease areas separated by normal mucosa) are strongly suggestive of CD. Typically, UC starts in the rectum and progresses proximally in a contiguous and circumferential fashion (Figure 3). However, UC may also be associated with inflammation in the cecum despite sparing of the ascending colon, as well as periappendiceal and appendiceal inflammation.[14-16]

Rectal sparing is typically seen in large-bowel CD, whereas UC is associated with confluent proctitis. However, endoscopic rectal sparing of inflammatory change was seen in 23% of children with newly diagnosed, untreated UC.[17] Markowitz and colleagues reported that mild patchy inflammation or normal mucosa was found in the initial rectal biopsies from 5 of 12 children with UC.[18] In another study, only one third of initial rectal biopsies from children showed well-developed IBD architectural changes in the mucosa. In this study of children, colonic mucosal biopsies obtained at the time of presentation showed less abnormality for all histologic criteria routinely used in the determination of chronicity and activity in colitis. This report also found a gradual change toward the adult phenotype in children older than 10 years of age.[19] Colonic inflammation may be less severe in children at presentation, leading to patchy inflammatory changes and rectal sparing, which are features classically associated with adult CD.[18,20,21]

Although terminal ileal involvement strongly favors the diagnosis of CD, it may also occur in some patients with UC. By definition, UC is confined to the colon, but it may be accompanied by superficial, mild, nonspecific mucosal inflammation in the terminal ileum, or backwash ileitis, in approximately 10% of pancolitic UC. The prevalence of backwash ileitis is similar in children and adults.[22] Although undefined histologically, backwash ileitis is regarded as mild, mixed inflammation in the lamina propria or crypts without crypt distortion, and contiguous active inflammation in the colon.[23] At endoscopy, a patient with backwash ileitis has erythematous, granular mucosa limited in length, proximal to a normal ileocecal valve, without strictures, stenosis, or ulceration. If nonspecific ileitis is identified, the term UC with backwash ileitis is appropriate.

The earliest endoscopic finding in UC is loss of normal vascular markings, followed by mucosal hyperaemia. Disease severity is worse distally. The mucosa becomes friable and bleeds easily with minimal endoscopic trauma. The disease may progress to form larger continuous ulcers. Inflammatory pseudopolyps can be seen in both CD and UC.[13] Loss of the normal vascular

pattern, mucosal folds, and haustral markings identify a chronic crypt destructive process. These features are not indicative of acute colitis or chronic nondestructive processes such as collagenous or lymphocytic colitis.[24] Very mild disease may appear normal or near normal at endoscopy, and biopsy may confirm the diagnosis.[25,26]

Upper gastrointestinal tract involvement is encountered particularly in CD. Up to 11% of adults have esophageal CD, and a similar percentage of children are affected.[27-29] Endoscopy may show deep ulcers, aphthous ulcers, nodules, and strictures suggestive of CD. Interestingly, there is some suggestion that esophageal involvement in CD may be a predictive factor for azathioprine usage in CD.[30] Several studies have proven the role of upper gastrointestinal endoscopy in the differentiation of CD from UC in children.[31,32] This has led to the current recommendation of routine upper endoscopy in the initial evaluation of suspected IBD,[3,4] which is in contrast to clinical practice in the adult population where such routine endoscopy is not recommended.[31]

These findings suggest that differentiation between CD and UC can be difficult in children. Not surprisingly, IBD without definite biopsy features of UC or CD is more common in this age group.[12] Some authors have reported IC characterized by onset during the first years of life, with rapid progression to pancolitis.[12,32] Clinically, this condition differs from the adult type associated with fulminant colitis, a condition in which the classic features of UC or CD disease may be obscured by severe ulceration.[33] Recent reviews have drawn attention to the historical use of the undefined term IC and its implications.[4,34] Opinion now favors use of the term IBD unclassified for those instances of IBD when definitive features of UC or CD are absent.[33,34]

Imaging has a well-established role in the diagnosis and localization of small-bowel involvement in IBD and, hence, in the differentiation of UC from CD. Barium radiography of the small bowel has been the conventional method for this purpose.[35] However, there is increasing evidence that magnetic resonance imaging can reliably show most lesions of CD and aid in the identification of transmural and extramural disease with the added advantage of avoiding radiation.[36] More recently, the role of capsule endoscopy has been highlighted due to its ability to detect otherwise unknown small-bowel lesions and more extensive small-bowel disease.[37] The sensitivity of this technique in identifying small-bowel disease appears to be superior to that of conventional barium radiography.

CD is differentiated from UC for prognostic and therapeutic reasons. UC is a more severe disease in children, and severe disease at presentation is a significant risk factor for colectomy.[15,38] Treatment strategies, including infliximab, are being developed to improve efficacy and avoid surgery.[39-41]

Every child suspected of having IBD should undergo diagnostic investigation. Recommended investigations include both upper gastrointestinal endoscopy and ileocolonoscopy with multiple biopsies. Small-bowel imaging should be undertaken in all cases unless the diagnosis is unequivocally UC.[3] Flexible endoscopy is safe, well tolerated, and effective in the management of children with IBD, and forms the first line of investigation. Biopsy findings are a more sensitive measure of disease extent than endoscopy, and biopsy of normal and abnormal mucosa is recommended.[25,42] Pathologists depend upon the endoscopist's description of the distribution of gross abnormalities and selection of the biopsy sites. Colonoscopy with examination of the terminal ileum together with multiple biopsies from all segments of the colon is an important part of the investigation and will greatly assist in the differentiation of CD from UC. Routine biopsies of the rectum, sigmoid colon, descending colon, transverse colon, cecum, and ileum are part of the investigation. Care should be taken to document the location of the biopsies obtained for histologic evaluation. Biopsy of the terminal ileum is invaluable in documenting the presence of disease, with deep ileal inflammation and granulomatous inflammation strongly favoring the diagnosis of CD.

## Histology

The histologic features of IBD are those of a chronic active colitis. Features of chronicity include crypt distortion, crypt branching, and a lymphoplasmacytic infiltrate deep to the crypts.[43] Variable numbers of eosinophils might be present. Paneth cell metaplasia on the left side of the colon is another indication of chronic disease. Activity is characterized by neutrophils in the lamina propria, epithelium, or within crypt lumens forming crypt abscesses. In more severe forms, there may be mucosal necrosis, ulceration, and inflammatory polyps with inflamed mucosa and chronic active inflammation in the lamina propria. Most mucosal biopsies from patients with allergic or infectious colitis lack typical features of chronic colitis.[44,45]

Architectural abnormalities and indicators of chronicity in IBD are often more lacking in initial colonic biopsies in the pediatric population.[20] This important difference may be related to a shorter duration of symptoms before the biopsy procedure. Children are more likely to present with a relatively acute onset of symptoms.[20,21] More prolonged histories are generally recorded in adolescents. The biopsy differences at presentation are largely confined to children less than 10 years of age in UC.[19] It has been found that as children approach

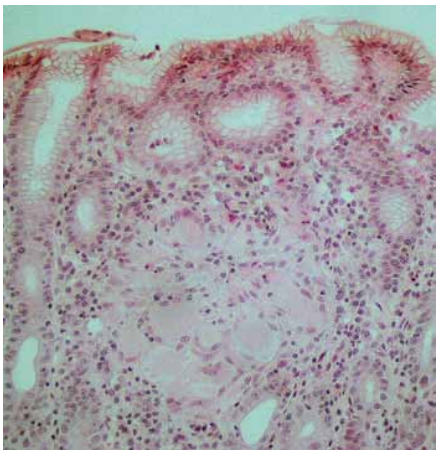

**Figure 4.** A well-defined Crohn's disease granuloma in the antrum.

adulthood the degree of inflammation and architectural distortion resembles that seen in adults.[19] Nevertheless, gastroenterologists and pathologists may be reluctant to diagnose a chronic disease in young children with limited histologic change in the absence of crypt distortion, as this may lead to an overdiagnosis of IBD.[46]

In UC, inflammatory changes are typically confined to the mucosa, whereas segmental and deep inflammation is typical of CD where the inflammation is transmural, with lymphoid aggregates extending to the subserosa. To the naked eye, the serosa has a dusky, granular appearance with creeping fat. Aphthous ulcers and tiny mucosal foci of chronic inflammation are the smallest lesions in patients with CD. These aphthous ulcers then connect and develop into linear ulcers across the transverse folds and divide the mucosa, forming lumps that result in a cobblestone appearance. Segments of inflamed and uninvolved mucosa are referred to as skip lesions. In CD, the inflammatory process is focal with inflamed areas bordered by normal crypts.[47] Fissural ulcers extending into the wall of the intestine are another feature of CD. However, the hallmark of CD is the nonnecrotizing sarcoid-like granuloma, particularly when found away from a crypt, in the deep submucosa, in lymphoid follicles, or in lymph nodes (Figure 4). It is important to note that, when seen in the vicinity of a crypt, these granulomas may be confused with the mucin granulomas associated with epithelial destruction.

In children, granulomas may also be seen in chronic granulomatous disease with pigmented macrophages in the lamina propria; common variable immune deficiency with its lack of plasma cells; and tuberculous infection with disproportionate submucosal inflammation and epithelioid histiocytes.[48-50] The frequency of granulomas is higher in children with Crohn's colitis even when the difference in the number of colonoscopic biopsies is taken into account.[51-53] Granulomas were identified in 61% of fully investigated pediatric patients at diagnosis, and 42% of these granulomas were found only in the terminal ileum and upper gastrointestinal tract, a finding that emphasizes the need to biopsy these sites.[51]

In a pediatric study, a significant proportion of children with new onset UC had patchy microscopic features of chronicity, with rectal sparing and little or no architectural distortion. This now-recognized rectal sparing phenomenon, in otherwise typical cases of UC, may cause confusion with CD.[21] In another study, the rectal biopsies in children did not differ with those from an adult control group.[19] Focal crypt atrophy is also less common in children.[20]

In colonic resections, microscopic inflammatory foci are common in grossly normal-appearing mucosa at surgical margins, raising the possibility of an increased recurrence rate. However, studies have concluded that the rate of recurrence is not increased by the presence of microscopic disease at the margins.[52-54] In general, it is recommended that only the grossly involved bowel should be resected.[55] Granulomas in the absence of associated inflammation at the margin are not considered clinically significant.

In children and adults, the histologic changes of early UC and CD differ from that of established disease, and the degree of clinical activity of disease correlates with the histologic degree of inflammation in UC and CD to a lesser extent.[56,57] In both groups, drugs used for treatment can induce mucosal healing, and the rectal mucosa may appear to revert to normal following therapy.[44,58,59] Mucosal involvement may become patchy or discontinuous, an appearance that closely resembles that seen in CD.[60] Post-treatment biopsies may also resemble those obtained in the early phases of IBD when crypt distortion may not be present.[61]

CD is particularly associated with inflammation of the upper part of the gastrointestinal tract. The performance of upper endoscopy in children with IBD has provided an additional diagnostic yield and guided the differentiation of disease type in many patients. In one study of children with IBD, some of the children with unaffected colons were diagnosed with CD solely on the basis of information from upper endoscopy.[62] Investigators suggested that, in the absence of *Helicobacter pylori* infection, focal chronic gastritis and active gastritis were evidence of CD in those patients with colitis (Figure 5).[63,64] In the stomach, characteristic focal mucosal collections of lymphocytes, sometimes accompanied by neutrophils with associated inflammatory damage to the epithelium, have been

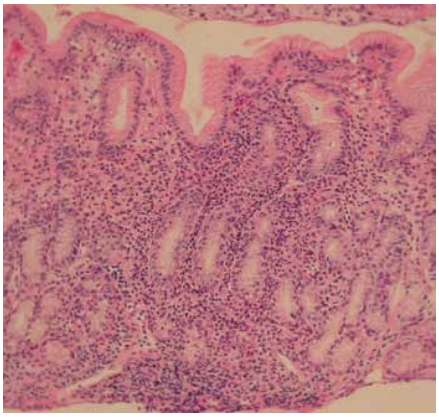

**Figure 5.** Focal antral inflammation in Crohn's disease.

referred to as focally enhanced gastritis.[65] In a review of upper gastrointestinal tract biopsies in children with CD, there was an increased incidence of gastric erosions with ulceration and histologic abnormalities. In addition, abnormal histology was noted in biopsy areas that appeared normal endoscopically.[66] These microscopic findings have defined the role of upper gastrointestinal endoscopy with biopsy in the investigation of IBD, particularly in the distinction of CD. Granulomas confirming the diagnosis of CD were found in the upper gastrointestinal tracts of 28% of children with CD. In some cases, granulomas were found solely in the upper gastrointestinal tracts.[67]

However, reports have described inflammatory changes in the stomach and proximal gastrointestinal tract of patients with UC as well; hence, pathology in the upper gastrointestinal tract should no longer exclude its diagnosis.[68] Ruuska and coworkers first drew attention to inflammatory changes in the upper gastrointestinal tract in 1994.[69] In the endoscopic and biopsy examinations of children with IBD, UC patients had esophagitis, nonspecific gastritis, gastric ulcers, and duodenal ulcers. Kaufman and associates reported chronic active gastritis in children initially diagnosed with CD, which was called UC after colectomy.[70] Chronic nonspecific inflammation is seen most frequently, whereas focal antritis in UC is uncommonly reported. Focal antritis, particularly if there are features of activity, is more suggestive of CD, but not diagnostic on its own.[68,71,72] In an adult population, focal periglandular inflammation was more frequent in CD (43% of 94 patients), but this pattern of inflammation was also seen in 12% of patients with UC and 19% of controls.[73]

Pascasio and colleagues reviewed 438 biopsies in children with gastritis looking for specific histopathologic parameters, including markers for CD such as focal neutrophilic glandulitis.[64] Of these cases, 58 were diagnosed as having CD by colonic biopsy and other standard criteria, 77% of which were predicted to have CD by gastric biopsy alone. In this study, none of the focal glandulitis biopsies had a history of UC. The prevalence of endoscopic esophageal CD in children was 7.6%, though histologic evidence is greater in children with colonic CD. Not all esophageal disease is associated with gastric lesions.[27]

## Summary

The differentiation between CD and UC has important therapeutic and prognostic implications. In the majority of cases, the differentiation is relatively straightforward. The presence of typical granulomatous inflammation in gastrointestinal biopsy specimens confirms CD in the appropriate clinical setting. In a substantial minority of children with CD, granulomas may be found only in upper gastrointestinal biopsies. This valuable information would be missed if routine upper endoscopy was not performed. When granulomas are not identified, a diagnosis of CD or UC can be suggested by the correlation of endoscopic findings with histology, combined with clinical and imaging information. Although no single endoscopic finding is pathognomonic, aphthous ulcers in any part of the gastrointestinal tract; endoscopic skip lesions; ulceration or stricturing of the terminal ileum; significant perianal disease; and biopsies showing features of IBD, particularly focal, favor CD. In UC, the inflammation is superficial and contiguous, extending from the rectum. In the majority of cases, childhood UC is a pancolitic process without skip lesions, with biopsies showing features of IBD.

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